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Age-specific familial risks for renal cell carcinoma with evidence on recessive heritable effects

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Age-specific familial risks for renal cell carcinoma with evidence on recessive heritable effects.

Background. Systematic comparisons of mode of inheritance for renal cell carcinoma (RCC) have not been carried out. The occurrence of cancer in parents and offspring may be due to dominant causes, whereas cancer affecting only siblings may indicate a recessive causation. Environmental effects need to be excluded.

Methods. The Swedish Family-Cancer Database includes all Swedes born after 1931 with their biologic parents, totaling 10.2 million persons. Cancer data were retrieved from the Swedish Cancer Registry from years 1961 to 2000, included 2415 cases of RCC in offspring and 18531 in parents. Standardized incidence ratios (SIRs) and 95% CI limits were calculated for offspring whose parents or sibling were diagnosed with RCC.

Results. The SIRs for siblings for RCC depended on their age difference. SIR was 7.63 (95% CI 3.63–14.08) when the age difference was less than 3 years and compared to 3.43 (95% CI 1.77–6.02) for large age difference. SIRs for familial risk of RCC were 1.73 (95% CI 1.31–2.26) when a parent and 4.58 (95% CI 2.87–6.94) when a sibling had RCC. Age-specific analysis of familial RCC among siblings revealed maxima at ages 40 to 49 and 60 to 68 years.

Conclusion. The findings in the present study offer evidence on recessive effects in early onset RCC.

Renal cell carcinoma (adenocarcinoma of the renal parenchyma) (RCC) is the most common cancer in the kidney, accounting for approximately 85% of all renal neoplasms. Most RCCs are of clear cell type and they harbor somatic mutations in the von Hippel Lindau (VHL) gene [1–4]. Risk factors of RCC include tobacco smoking, obesity, components of diet, some occupational exposures, and family history [5–9]. Over 2% of the Swedish RCC patients have a parent with RCC, and the familial risk has been about 1.6 in Sweden and the United States [10–12]. RCC is a manifestation in VHL syndrome, affecting half of mutation carriers in the VHL gene; central nervous system hemangioblastomas, and ocular angiomas are other manifestations in VHL disease [13–16]. RCC is also related to rare familial clusters with or without chromosome 3 translocations and other syndromes, such as tuberous sclerosis and Birt-Hogg-Dube syndrome [17–19]. The inheritance of RCC is dominant in these cancer syndromes and parent-to-offspring transmission is also detected in population-based studies on familial aggregation of RCC [10–12]. However, risk for RCC among siblings has been higher than that between offspring and parents, which could indicate some contribution by a recessive mode of inheritance [20–23].

The aim of the present study is to carry out an age-specific analysis of familial RCC using the newest update of the nation-wide Swedish Family-Cancer Database [24]. We want particularly to investigate the role of possible recessive effects in RCC, which are inferred when the risks among siblings without affected parents exceed the risks for offspring of affected parents. The results would propose an entirely new strategy for gene identification efforts. However, the inference is guarded by childhood shared environmental effects, because they increase familial risk among siblings, which makes them indistinguishable from recessive effects [25, 26]. We believe that the comparison of familial risks between siblings according to their age difference is a solution to this problem; to our knowledge such analysis is novel for RCC. The Database covers over 10 million people registered in families and 1 million medically verified cancers, providing excellent opportunities for genetic epidemiology.

METHODS

Statistics Sweden maintains a "Multigeneration Register" where children, offspring, born in Sweden in 1932 and later, are registered with their parents (those pleading parenthood at birth) and they are organized as families [24]. Information on the database is also available at the Nature Genetics website as 'Supplementary

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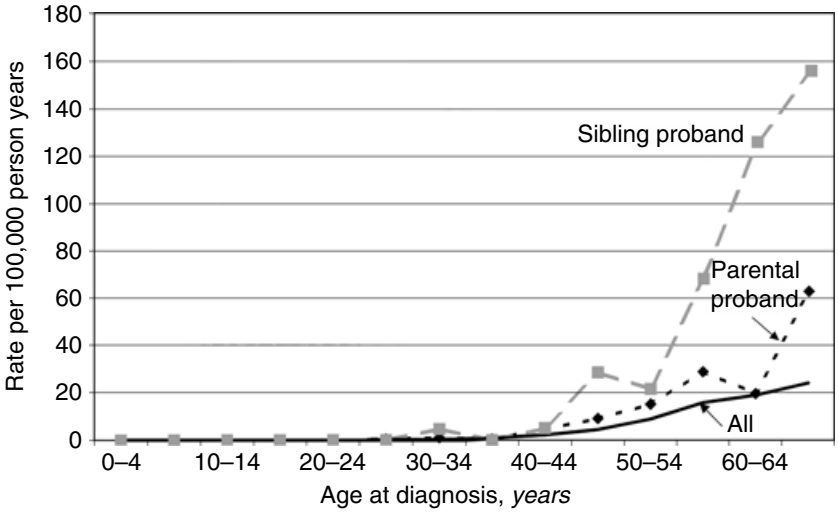

Fig. 1. Age-specific incidence of renal cell carcinoma (RCC) in offspring of parental and sibling probands.

information' [27]. The data on families and cancers have a complete coverage, baring some groups of deceased offspring, which affect those born in the 1930s and who died before 1991. Although this small group of offspring with missing links to parents has negligible effect on the estimates of familial risk [28], we limited the present study to offspring whose parents were known, to eliminate possibility of bias. This "Multigeneration Register" was linked by the individually unique national registration number to the Cancer Registry from years 1958 to 2000. Cancer registration is considered to be close to 100% currently [29]. Only the first primary RCCs were considered. A four-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7) was used; the code 1800 was used for RCC. The histologic classification of RCCs was used, as present in the Cancer Registry, to define adenocarinoma (pathology codes 096) and Wilms' tumor (886); only adenocarcinoma was included. These codes have been used since the start of cancer registration in Sweden (WHO/HS/CANC/24.1 Histology Code). From year 1993 onward, ICD-O-2/ICD with histopathologic data according to the Systematized Nomenclature of Medicine (SNOMED) (*http://snomed.org*) was used.

Standardized incidence ratios (SIRs) were used to measure cancer risks for offspring according to occurrence of cancers in their families. When more than two affected offspring were found in any family, they were counted as independent events. No family with multiple affected siblings had an affected parent. SIRs were calculated for offspring whose parent or sibling had the same, concordant cancer (i.e., using parents or siblings as probands). Follow-up was started for each offspring at birth, immigration, or January 1, 1961, whichever came latest. Follow-up was terminated on diagnosis of first cancer, death, emigration, or the closing date of the study, December 31, 2000.

Parents' ages were not limited but offspring were 0 to 68 years of age. All tumor incidence rates were based on the data in the Family-Cancer Database, and they were essentially similar to rates in the Swedish Cancer Registry. Rates were standardized to the European population. SIRs were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year age, gender, tumor type, period (5-year bands), socioeconomic status (six groups, including farmers, manual workers, blue collar workers, professionals, self employed, and others), and residential area (three groups, including the three largest cities of Stockholm, Gothenburg, and Malmo, southern counties and northern counties), specific standard incidence rates for all offspring lacking a family history [30]. Confidence intervals (95% CI) were calculated assuming a Poisson distribution [30]. Risks for siblings were calculated using the cohort method, described elsewhere [20]. This method is not sensitive to the sibship size [20]; however, based on a previous analysis from the Database, neither sibship size nor birth order are related to risk of RCC [31]. The analysis of this study was implemented in the environment of the SAS, release 8.2.

RESULTS

The Family-Cancer Database covered years 1961 to 2000 from the Swedish Cancer Registry and it included 1516 sons and 899 daughters RCCs between ages 0 to 68 years, in addition to 11137 fathers and 7394 mothers RCCs. Age-specific incidence rates of RCC in offspring according to family history are shown in Figure 1. Early onset incidence maximum for RCC among siblings occurred at ages 30 to 34 and 45 to 49 years; offspring of affected parents showed a peak incidence at 50 to 59 years.

Table 1 presents the risk for RCC among siblings according to their age difference. Age difference associated

Table 1. Standardized incidence ratio (SIR) for renal cell carcinoma (RCC) in siblings by age difference

Age at diagnosis *years*	Sibling ages < 3 years				Sibling ages ≥ 3 years			
	Observed	SIR	95% CI		Observed	SIR	95% CI	
<50	2	5.95	0.56	21.87	5	**4.44**	**1.40**	**10.43**
≥50	8	**8.21**	**3.51**	**16.25**	7	**2.96**	**1.17**	**6.13**
All	10	**7.63**	**3.63**	**14.08**	12	**3.43**	**1.77**	**6.02**

Bold type signifies 95% CIs do not include 1.00.

Table 2. Standardized incidence ratio (SIR) for renal cell carcinoma (RCC) in offspring of parents and sibling probands

Age at diagnosis *years*	Parental proband				Sibling proband				SIR ratio (sibling/parent)
	Observed	SIR	95% CI		Observed	SIR	95% CI		
<50	22	**1.87**	**1.17**	**2.84**	7	**4.78**	**1.90**	**9.91**	2.6
≥50	33	**1.65**	**1.14**	**2.33**	15	**4.49**	**2.50**	**7.42**	2.7
All	55	**1.73**	**1.31**	**2.26**	22	**4.58**	**2.87**	**6.94**	2.6

Bold type signifies 95% CIs do not include 1.00.

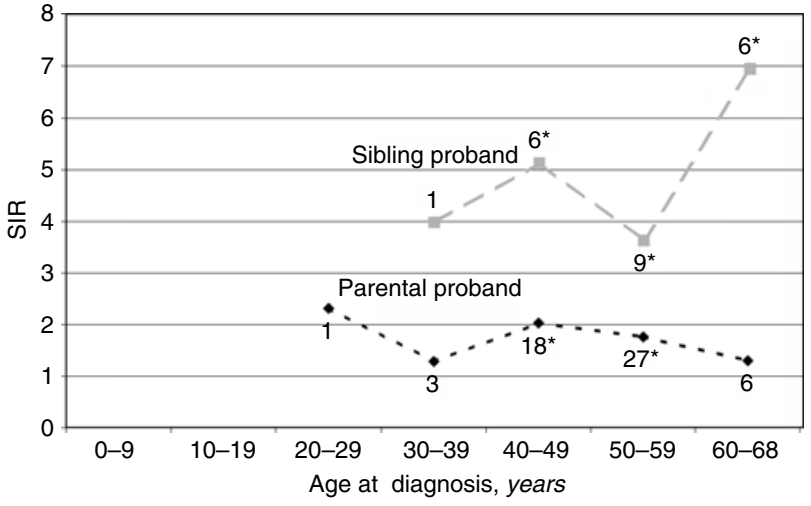

Fig. 2. Familial standardized incidence ratio (SIR) for offspring renal cell carcinoma (RCC) when parents or siblings were probands. The numbers indicate the number of cases and the stars show that the 95% CIs do not include 1.00.

with the risk of cancer. Those born less than 3 years apart had higher risks. Among those born with a large age difference, the risk was twofold higher in the young age group (diagnoses before age 50 years) than in the older one. Among the total of 22 affected siblings, two were diagnosed with a second primary brain hemangioblastoma (ages at diagnosis of first primary RCC were 45 and 50 years; diagnostic ages for the second primary brain hemangioblastomas were 50 and 54 years, respectively).

Age-specific familial risks for RCC were analyzed using parents or siblings as probands (Table 2). The overall SIRs were 1.73 (95% CI 1.31–2.26) and 4.58 (95% CI 2.87–6.94), respectively. These were approximately 2.5-fold higher among siblings than between offspring and parents. The SNOMED histology was available only from year 1993 onward, and thus few cases were retrieved. For clear cell adenocarcinoma, the SIR was 2.99 ($N = 12$, 95% CI 1.54–5.34) when a parent had RCC. Only two affected sibling pairs were identified. Among the 12 clear cell adenocarcinoma families, other cancers included prostate, liver, thyroid, and cervical cancer, one case in each family member.

Figure 2 shows the age-specific SIRs for RCC when parents or siblings were used as probands. The SIRs showed a prominent early age onset maximum between ages 40 to 49 years when siblings (SIR = 5.13, 95% CI 1.85–11.25) or parents were probands (SIR = 2.03, 95% CI 1.20–3.21). The proportion of familial cases belonging to the early onset component up to the age 50 years was 32% and 40% by sibling or parental proband, respectively.

In the Database, eight families had an offspring affected by first primary brain hemangioblastoma and second primary RCC. Because the present study only covered first primary cancers, these RCCs were not included in the analysis.

DISCUSSION

Familial aggregation of cancer may be due to environmental factors shared by family members or due to shared

genes [25, 32]. The risk of kidney cancer shows no correlation between spouses, suggesting that there are no strong environmental factors that could explain the familial aggregation. However, spouse concordance will not detect environmental sharing early in life. Migrant studies from Sweden show that the patterns for most cancers, including kidney cancer, in immigrants are largely set during the two first decades of life [33, 34]. For these reasons, we considered important to examine the possible effects of shared childhood environment, which we accomplished by comparing risks for RCC between siblings according to their age difference. The results suggested that there was an effect of age difference in cancers diagnosed after age 50 years but not in those diagnosed before. We conclude that childhood sharing is probably not important for RCC diagnosed before age 50 years.

A larger familial risk among siblings whose parents were unaffected compared to offspring of affected parents, as shown in the present study, would provide evidence on a recessive effect. However, such data fail to discriminate between recessive and X-linked inheritance. If a disease was X-linked, it would affect mainly men. For RCC a large X-linked effect is unlikely because a recent study from this Database showed that there was no gender effect in familial kidney cancer [35]. We thus conclude that our data provide evidence of recessive inheritance, at least in early-onset RCC.

A dominant predisposition to RCC in association with VHL disease is well documented and 24% to 45% of patients with a mutated *VHL* gene develop clear cell RCC during their lives [36]. In the present analysis, we found only two RCC cases among the siblings (2/22 = 9%) with features of a VHL disease [36]. The high familial clustering of RCC among siblings is therefore unlikely to be explained by the occurrence of the VHL disease. Because even the other known familial clusters of RCC, including chromosome 3 translocations, tuberous sclerosis, and Birt-Hogg-Dube syndrome, show dominant inheritance, we suggest that our findings point to a yet unknown recessive condition [17–19].

There has been no population-based studies on recessive effects in RCC, which probably explains the current lack of knowledge in this area. The detection of recessive conditions is difficult because the cases appear apparently randomly in pedigrees but often reveal consanguinity at a closer inspection. Population geneticists have raised questions about the relatively small number of known human recessive syndromes. In species of experimental animals recessive traits predominate as opposed to humans where dominant traits are more common [37].

CONCLUSION

The present study offers further evidence of recessive susceptibility genes in early-onset RCC [23]. Unfortunately, individuals in the Family-Cancer Database are anonymous and we have no direct possibility to search for possible consanguinity in the affected families. If consanguinity was confirmed, the strategy for finding the putative recessive gene(s) would be mapping for homozygosity for alleles in the affected individuals.

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